REMARKS

Claims 1-17, of which claims 4-6 and 9-11 are currently amended and claims 12-17 are new, appear in the application for the Examiner's review and consideration. Claims 4-6 and 9-11 are amended for clarity in light of the state of the art. New claims 12-17 are rewritten versions of, and are supported by, the original claims and the specification. In particular, claim 12 is added to recite only the elected peptide species, claims 13-16 are rewritten versions of claims 1-3 and 7 as dependent from the product claim 12 and new claim 17 is directed to salt forms of the peptide of claim 8. The specification is amended to correct an informality. As no new matter has been introduced, Applicants respectfully request that the amendments be entered at this time.

In response to the Examiner's comments on the restriction requirement, Applicants confirm their election with traverse.

Instead of being directed to different inventions, the present peptide compounds of Groups XX through XXXVI share structural and functional properties in that they are all peptides containing a sequence of a CDR of the heavy or light chain of an anti-p53 mAb and are capable of eliciting antibodies to p53. Although the peptides include variant structural elements, the peptides are simply different species of, and support the patentability of, the generic peptide described in claim 8, and not different inventions such that a restriction requirement is warranted. The fact that all the peptides belong to the same class and subclass underscores this point.

The Examiner states that the literature search is not co-extensive and is much more important in evaluating the burden of search than the classification of the subject matter. Although the literature search may not be completely co-extensive, Applicants believe that the breadth of the search would not be such that a restriction is required for each peptide sequence, especially considering the common structural and functional characteristics of the present peptides.

The specific peptides also each enable and support the method claims as explained in the previous response of March 25, 2004. As the method claims relate to, and are enabled by, the use of the specific peptides, the peptides and the methods are related such that a proper search of the peptide claims would lead to art relating to the use of the peptides and a search of the methods would result in identification of peptides used in such methods.

It is therefore respectfully submitted that the restriction requirement is in error and should be withdrawn so that all aspects of the claims are examined together in this

application. In the interest of expediting the prosecution of this application, however, new claim 12 is added to recite only the elected peptides of SEQ ID NO:21 and SEQ ID NO:11. In accordance with the Examiner's previous comments of March 1, 2004 regarding rejoinder of process claims, new claims 13-16, which are rewritten versions of original claims 1-3 and 7, are also added and depend from claim 12. As the following explanation shows, these claims are believed to be allowable.

The specification is objected to for the informalities stated on page 3 of the Office Action. In response, an appropriate correction is made and the objection should be withdrawn.

Claims 8-11 are objected to for encompassing non-elected inventions. Although Applicants traverse this objection in light of the preceding explanation with respect to the restriction requirement, new claim 12 is added in the interest of expediting the prosecution of this application. As noted above, new claim 12 recites only SEQ ID NO:21 and SEQ ID NO:11 and, since it encompasses only the elected species, this claim is considered allowable.

Claims 8-11 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons stated on page 4 of the Office Action. Applicants respectfully traverse.

With respect to the recitation "and salts and chemical derivatives thereof," paragraphs [0056]-[0057] of the specification clearly define the scope of the terms "chemical derivatives" and "salts." Paragraph [0056] defines a "chemical derivative" of a peptide as "contain[ing] additional chemical moieties not normally a part of the peptide," including "[c]ovalent modifications of the peptides." The specification explains that "[s]uch modifications may be introduced into the molecule by reacting targeted amino acid residues of the peptide with an organic derivatizing agent that is capable of reacting with selected side chains or terminal residues," and lists "esters, N-acyl derivatives, and the like" as examples. Similarly, paragraph [0057] explains that the scope of the invention also includes "salts, both organic and inorganic, of the CDR-based peptides." Further, Applicants believe that it is clear from the plain reading of claim 8 that the phrase "and salts and chemical derivatives thereof" means a compound claim wherein the peptide is a derivative or salt form. Since the meaning of the recitation is clear from the claim itself, as well as from the specification, the claim rejection should be withdrawn.

Furthermore, this rejection is not applicable to claim 17 which recites the salt forms of the peptide.

Applicants also respectfully submit that the recitation "eliciting antibodies to p53" in claim 8 is clear. As explained in the specification, the present invention relates to "the use of an Ab1 anti-p53 mAb to generate an Ab3 anti-p53 response" (paragraph [0038]). Claims 8-11 are in fact directed to peptide species containing idiotypic determinants such as sequences from a CDR of such Ab1 anti-p53 mAb which also elicit an Ab3 anti-p53 response, and the meaning of the phrase "eliciting antibodies to p53" in claim 8 is thus clear from the disclosures.

Therefore, all the rejections under § 112, second paragraph, should be withdrawn.

Claims 8-11 are also rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement for the reasons stated on pages 4-5 of the Office Action. Applicants respectfully traverse.

Applicants first wish to point out that only the species that are examined, and not every individual species within the scope of the claim, need to be demonstrated to exhibit a certain feature, for example, the capability of eliciting an immune response to p53. As both SEQ ID NO:11 and SEQ ID NO:21 are explained to be able to elicit anti-p53 Abs, a peptide based on the CDR3 of the light chain (240VL) of the anti-p53 mAb 240 that contains SEQ ID NO:11 or SEQ ID NO:21, or is derived from either of these sequences, can be reasonably expected to also elicit the production of anti-p53 Abs. For instance, as the specification demonstrates that SEQ ID NO:11 is sufficient to induce the anti-p53 response, it is also reasonable to expect that a peptide preferably having 9-30 amino acid residues (as defined in paragraph [0058]) and containing SEQ ID NO:11 will also elicit the production of anti-p53 Abs. Thus, the specification provides a sufficient definition of the peptide structure (i.e., a peptide based on the CDR3 of the light chain of the anti-p53 mAb 240 that contains SEQ ID NO:11 or 21, or is derived from either) such that one skilled in the art would understand that Applicants had possession of the claimed invention at the time the application was filed. Accordingly, the specification provides an adequate written description, and this claim rejection should be withdrawn.

Likewise, the§ 112 rejection of claims 8-11 for the reasons stated on pages 5-7 of the Office Action should also be withdrawn.

The Examiner states that the specification "does not teach production of anti-p53 antibodies" but "teaches production of anti-idiotype antibodies for an anti-tumor response" and that the specification "does not teach production of an anti-id response with just any CDR peptide or any chemical derivative thereof" (p. 6, Office Action). Contrary to these

statements, the specification does teach production of anti-53 antibodies. For example, paragraph [0104] in Example 4 discloses production of anti-p53 Abs by SEQ ID NO:21 (peptide V) ("The incidence of mice developing IgG anti-p53 antibodies (ELISA assay) was 8/10 and 7/10 for peptides V and VI, the CDR3-based peptides of mAb 240 and mAb 421, respectively"). Table 4 also demonstrates that mice immunized with peptides V-IX rejected the Meth A tumor, thereby showing that fragments of CDR-based peptides can be used to induce anti-p53 immunity. In addition, since the critical peptide sequences are present in salts and chemical derivatives of the present peptides, which provide the peptides in different chemical form only (i.e., in salt form or with additional chemical moieties), a person skilled in the art would readily understand that the salts and chemical derivatives of the peptides have the same immunological properties as the peptides themselves. Therefore, the specification is enabling as to a peptide that contains a CDR sequence from an anti-p53 antibody and is capable of eliciting an immune response to p53, as well as to salts and chemical derivatives thereof.

The Examiner cites Erez-Alon *et al.* (Cancer Res. 58:5447-5452, 1998) as teaching that "not all peptides from a CDR of an anti-p53 antibody are capable of eliciting an immune response against p53" (pp. 6-7, Office Action). Although some experiments presented in Erez-Alon, which was published after the foreign priority date of this application, shows that immunization with peptides based on CDR of 248 pAb did not induce anti-p53 immunity, this reference also shows that the 248 pAb itself did *not* substantially induce an AB3 response but only induced an AB2 response. Hence, this reference does not demonstrate that "not all CDRs from an anti-p53 antibody can elicit anti-p53 antibodies" as the Examiner contends, but it is reasonable to expect that all peptides based on CDRs from the Abs that induce an anti-p53 response will also induce an anti-p53 response.

In addition, claims 4-6 and 9-11 have been amended for clarification to exclude 248 mAb, which Applicants have found, since filing this application, not to elicit the desired anti-p53 response. Thus, Applicants respectfully submit that the specification, in view of the state of the art and further in view of the claim amendments, provides enablement for peptides capable of eliciting antibodies to p53 such that a person skilled in the art can identify the peptides that would induce anti-p53 immunity without undue experimentation.

Furthermore, the Examiner's statement that "there are antibodies that have CDR sequences that are in anti-p53 antibodies that do not bind p53 in other antibodies" (p. 7, Office Action) is incorrect. The Examiner cites EP 0438312 A2 (Law *et al.*) as teaching "the

exact sequence of SEQ ID NO:21 and 11" and that "the sequence is from CDR3 of an anti-CD18 antibody." However, the sequence containing SEQ ID NO:21 and 11 as disclosed in Law is *not* a sequence of the expressed anti-CD18 antibody. Law discloses a sequence containing SEQ ID NO:21 and 11, but identifies a sequence that does not contain SEQ ID NO:21 and 11 as the actual sequence of the MAb 1B4 light chain ("A unique DNA sequence representing a murine IgG2a heavy chain variable region was obtained, but two kappa light chain variable regions were represented within the cloned population (Figure 3). . . . 1B4 light chain -2 (Figure 25) was deemed to be the actual sequence of the MAb 1B4 light chain. This is consistent with the determined DNA sequence of the light chain-1 molecule (Figure 24) which suggests it represents a murine kappa light chain variable region of subgroup III containing a mutation in the CDR3/FR4 region whose consequence is peptide chain termination" (col. 20, line 50 to col. 21, line11)). Hence, the sequence containing SEQ ID NO:21 and 11 is, in fact, not a sequence of the expressed anti-CD18 antibody according to the Law disclosure, and the prior art does *not* demonstrate that the CDR sequences are not specific for anti-p53 antibodies.

As the preceding explanation shows, therefore, the specification provides sufficient guidance and enablement for one skilled in the art to carry out the invention without undue experimentation, and Applicants respectfully request that § 112, first paragraph, rejection be withdrawn.

Claims 8-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Jannot *et al.* (BBRC 230:242-246, 1/1997) for the reasons set forth on pages 8-9 of the Office Action. Applicants respectfully traverse.

Applicants first note that, contrary to the Examiner's statement, the present specification does in fact disclose the length of the peptides at paragraph [0058], which provides: "The peptides according to the invention have preferably 9-30 amino acid residues, examples of which are the 17- to 21-mer peptides V, VI, VII, VIII and IX, which are based on the CDR sequences mentioned above . . . " Since the specification discloses the length of the peptides, the VL does not read on the present claims.

Further, Jannot merely teaches that the single-chain antibody scFv-421 specifically binds the tumor suppressor protein p53. By contrast, the present invention is directed to the peptides based on the CDR of anti-p53 Abs that are capable of eliciting antibodies to p53, and therefore substantially differ from disclosures made in Jannot. As the specification explains at paragraph [0032]: "The anti-p53 mAb fragments that can be used according to the

invention include antigen-binding fragments (Fab), F(ab')2 or any other type of antibody molecule, including single chain Fv fragments of antibodies, as long as such antibody fragments are able to bind p53 *as well as* peptides based on a CDR of the heavy or light chain of an anti-p53 mAb, which peptides are *capable of eliciting antibodies to the p53 without necessarily binding p53*" (emphasis added). Hence, a reference that merely teaches the specific binding of scFv-421 to p53 does not anticipate the present claims which are directed to peptides that are capable of eliciting antibodies to p53.

Moreover, Jannot describes only the construction and expression of an scFv based on the anti-p53 pAb 421, and does not describe immunization with anti-p53 fragments to induce anti-p53 antibodies or anti-tumor immunity. The Examiner states that, since the peptide of the present invention is from an anti-p53 mAb, it would inherently produce anti-idiotypic antibodies (p. 9, Office Action). This conclusion, however, fails to recognize the complexities of p53 immunity. As explained in the specification, immunity to p53 molecule has two attributes of interest: (a) anti-DNA antibodies by an anti-id network, since p53 binds DNA and anti-p53 antibodies may induce anti-DNA antibodies as anti-ids; and (b) anti-tumor effect, since p53 accumulates in transformed cells ([0040]). The present application discloses that "[t]he induction of specific anti-DAN antibodies by immunization with a mAb to the domain of p53 that binds specific DNA indicates that anti-DNA antibodies can indeed arise by an anti-id network," thus showing that "the anti-id network appears to preserve structural similarity with particular p53 domains" ([0044]). Thus, according to the present invention, immunization either with an anti-mutant p53 mAb, an anti-wild type p53 mAb, or an mAb against both the wild type and mutant p53 induces anti-p53 antibody titers, apparently by way of an anti-idiotypic network ([0045]). However, because the development of specific anti-DNA antibodies (Ab2) varies with the domain of p53 recognized by the Ab1 that is used to activate the network, sequence-specific anti-DNA antibodies can be produced by immunization with anti-p53 mAbs specific to the central DNA-binding domain of p53, and generations of anti-DNA antibodies can be avoided by using an anti-p53 antibody that does not bind a domain of p53 that binds to DNA ([0046]). The finding that the peptides from anti-p53 mAbs also induce anti-p53 antibodies and anti-tumor immunity is therefore a novel feature of the present invention and is not anticipated by the prior art.

Accordingly, since Jannot does not anticipate each and every element of the present claims 8-10, Applicants respectfully request the § 102 rejection be withdrawn.

In view of the foregoing, it is believed that the entire application is now in condition for allowance, early notification of such would be appreciated. Should the Examiner not agree, a personal or telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the claims. Please call the undersigned to expedite the allowance of all the claims in this application.

Respectfully submitted,

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